Remarks

Claims 2-3, 6-28, and 30-36, and 38-45 are pending. Claim 2 has been amended. This amendment is supported by the specification as originally filed and no new matter is introduced. All pages referenced herein are to the published application, US Patent Application Publication No. 2004/0086490.

Claim Objections

Claims 43-45 were objected to for reciting a two-vector system but only describing what the first vector comprises. The objection appears to be based on the fact that these claims recite a vector system comprising "two vectors" without mention of the second vector. In response, these claims have thus been amended to recite a vector system comprising "a first and second vector."

Rejection Under 35 U.S.C. § 112, first paragraph

A. Claims 2-3, 6-28, and 30-36, and 38-45 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection.

First, Applicants note that the Examiner has inappropriately combined arguments supporting the Written Description and Enablement rejections together in the Office Action. As a result, the Examiner has used language relevant for enablement in the context of written description arguments. While these requirements stem from the same paragraph of the statute, they represent different standards and should not be confused. Applicants have therefore attempted to respond to each rejection independently based on the correct standard for each.

The Office Action posits that claims lack written description for a genus of AAV4 proteins claimed by percent homology to a reference sequence. According to the Office Action, these claims are directed to a genus of proteins based on homology "without any correlation between structure and function" and an "arbitrary structural relationship between the claimed

protein sequence(s) and the single disclosed species of amino acid sequences." Applicants respectfully disagree.

As noted by the Examiner, the written description requirement for a genus may be satisfied by "sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics." Thus, description of a genus by structure, e.g., amino acid sequence, can stand alone to provide sufficient description of a representative number of species of the genus. If Applicants are relying on structure and not function to define the genus, then it is not necessary to provide any correlation between structure and function in order to satisfy the written description requirement. It is on this point that the Examiner appears to be misapply the law, i.e., by requiring description above-and-beyond a structural description.

For example, the Office Action, citing *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.* (927 F.2d 1200 (Fed. Cir. 1991)), *Fiers v. Revel* (984 F.2d 1164 (Fed. Cir. 1993)), *Fiddes v. Baird* (30 USPQ2d 1482 (BPAI 1993)), and *Regents of the Univ. Calif. v. Eli Lilly & Co.* (43 USCQ2d 1398 (Fed. Cir. 1997)), notes that the court and Board have repeatedly held that:

> ...an adequate written description of a biological sequence requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the sequence itself. It is not sufficient to define a protein solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any proteins with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what the material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid or protein, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the protein has been isolated. Thus, claiming all proteins that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived.

(page 4 of Office Action, emphasis added). While Applicants agree with the Examiner that the above is an accurate statement of the law, it is also an indication that the Examiner does not fully appreciate the significant difference between attempting to claim a genus of proteins by function (biological property) and claiming it by sequence identity (structure).

The above cases stand for the proposition that you can not claim a protein by reference merely to its function (biological property). For example, Applicants in *Baird* claimed a DNA sequence encoding mammalian FGF but only taught a DNA sequences for bovine pituitary FGF. 30 U.S.P.Q.2d at 1481. Thus, neither the applicant nor the skilled artisan could have predicted what sequences would fall within the scope of the genus claim since a representative number of species were not provided to set the metes and bounds of the genus.

Likewise, Applicants in *Lilly* were attempting to claim human cDNA for human proinsulin while only providing the sequence for the rat cDNA. 119 F.3d at 1566. As the sequence of human proinsulin was not known at the time that application was filed, the skilled artisan could not have known what was actually being claimed. The court therefore concluded that applicants were attempting to claim the coding sequence based only on an indication of what the gene does rather than what it is. *Id.* at 1568. This is clearly an example of an attempt to claim a genetic sequence entirely by its function rather than its structure.

Similarly, Applicants in *Amgen* claimed a purified and isolated DNA sequence encoding human EPO prior to the DNA sequence for EPO being known. 927 F.2d at 1206. The court concluded that it is not sufficient to define a chemical compound solely by its principal biological property, e.g., encoding human EPO. *Id.* This is also clearly an example of an attempt to claim a genetic sequence entirely by its function rather than its structure.

Finally, Applicants in *Fiers* were attempting to establish conception for DNA encoding human fibroblast IFN-β polypeptide based on proposed protocols for isolating this DNA. 984 F.2d at 1167. The court concluded that conception did not occur for a claim to the DNA *per se* until one has a mental picture of the structure, i.e., sequence. *Id.* at 1169. Interestingly, the court opined that conception may occur when one is able to define a chemical by its method of preparation, but only if the chemical is claimed by its method of preparation. *Id.* Thus, the court concluded that "an adequate written description of a DNA requires more than a mere statement

that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1170. Again, this is an example of an attempt to claim a genetic sequence based entirely on its function and a means for isolating it.

The Office Action, however, attempts to characterize *Baird* and *Lilly* as representing "an attempt to claim unknown subject matter (human sequences) only by homology to what is actually disclosed (rat or bovine sequences)" and posits that the instant claims are similarly "reach-through" claims, attempting to claim subject matter not specifically disclosed. Applicants respectfully disagree that that is a fair characterization of the holdings in those cases. Again, there is a large difference between claiming a genetic sequence based entirely on its function (e.g., gene name, what it encodes, and/or method of isolation) and claiming a genetic sequence based on percent identity to a reference sequence. In the former case, the genus is defined entirely by function, whereas in the latter case the genus is defined completely by structure.

Consistently, in Example 11A of the new USPTO *Written Description Training Materials* ("*Training Materials*"; March 25, 2008 Rev. 1), a claim to "an isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to SEQ ID NO:2" was concluded to satisfy the written description requirement because "with the aid of a computer, one of skill in the art could have identified all of the nucleic acids that encode a polypeptide with at least 85% sequence identity with SEQ ID NO:2." It is therefore factually and legally incorrect to assert that the instant claims are attempting to claim the genus by function or a mere wish or plan instead of describing the genus by structure.

Rather than address the merits of this distinction, the Examiner's response was to argue that "the Guidelines are not rule making and are not binding." However, the Examiner does not provide any reason why the instant claims are distinct from those of the *Training Materials*. Instead, the Examiner has argued that the *Training Materials* are not applicable because it did not take into account the Examiner's reasoning, which apparently involves mathematics.

According to the Office Action, for a 734 amino acid reference sequence, the number of possible sequences having 72 amino acid substitutions (90%) relative to the reference is approximately 1.5×10^{190}. The Examiner points to this large number of species within the genus and argues that the specification provides no guidance in determining which polypeptide variants

would be functional. However, even if *arguendo* this were true, it would not negate possession of the genus as posited by the Examiner. Rather, as noted above, the Examiner appears to be mixing written description and enablement standards to support his position, since whether variants covered by the claims are functional is a question of enablement and not possession. In other words, the Examiner appears to be improperly arguing that the claims lack written description because Applicants have allegedly not provided sufficient guidance as to which of the variants have the desired function.

Applicants respectfully assert that the written description requirement is satisfied in the instant claims since the genus of sequences are described based entirely on their structure and not based on their function. As such, there is no basis in law for the Examiner to require Applicants to provide any correlation between structure and function in order to demonstrate that Applicants were in possession of the genus of sequences at the time the application was filed.

Applicants identified and characterized a novel AAV (AAV4) with unique tissue tropisms. Based on this finding, Applicants further conceived of viral vectors comprising AAV4 nucleic acids for use in delivering nucleic acids to cells. However, a claim limited to the exact AAV4 sequences has little value since the ability to identify conservative amino acid substitutions is routine in the art. A competitor could simply modify a few amino acids and circumvent Applicant's rights. It is therefore reasonable for Applicants to claim a genus of amino acid sequences based on this ability to make modifications to the sequence with a reasonable expectation at arriving at a functional variant. The only reasonable issue should be the breadth of the genus the Applicant is attempting to claim based on the predictability of finding a functional variant and the skill in the art, which are relevant concerns under the enablement requirement. However, when the genus is described entirely by reference to structure, there is no basis for applying a written description rejection to the claims. Applicants therefore respectfully request the withdrawal of this rejection.

B. Claims 2-3, 6-28, and 31-36, and 38-45 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Specifically, the Examiner appears to be taking the position that claims reciting a genus of amino acid sequences based on sequence identity (even as high as

99%) to a reference sequence can not be enabled where only the reference sequence has been shown to be functional. While Applicants recognize that enablement is the proper basis for evaluating the breadth of a genus of amino acid sequences, Applicants respectfully assert that the skilled artisan can make and use the claimed vector systems without undue experimentation using amino acid sequences having at least 90% sequence identity to the reference sequences. Applicants therefore respectfully traverse this rejection.

The Office action appears to base this rejection on the alleged failure of the application to teach how to make and test 3×10^{192} possible protein variants, as if the skilled artisan attempting to practice the instant claims would actually be faced with this dilemma. While Applicants agree that the claims have to be enabled for their full scope, there is a difference between enabling the full scope of the claim and enabling the skilled artisan to actually practice each and every embodiment covered by the claims. Of course, a claim that required a skilled artisan to make and test 3×10^{192} variants in order to arrive at a functional variant would fall well short of enablement, but that is not the case here. At best, the Examiner has provided evidence that some variants will not be functional such that the skilled artisan may have to make and test a few variants within the large genus before arriving at one that is functional. However, even if *arguendo* it were shown that only 50% of the variants within the genus were functional, the skilled artisan would still only have to test a few variants to find one that was functional. Thus, the issue is not whether the genus is large (or even humongous) or whether there are inoperable embodiments; rather the issue is whether the skilled artisan would have to engage in undue experimentation in order to practice the invention, which in the instant case requires making and using one (1) functional variant covered by the claims.

Applicants have provided evidence for the general predictability for maintaining function at sequence identities above 70% (see Tian, W. and Skolnick, J. J Mol Biol. 2003 Oct 31;333(4):863-82, of record). Specifically, Tian and Skolnick evaluated the predictability of the enzyme commission (EC) number for proteins based on sequence identity. The EC number is numerical classification scheme for enzymes based on the chemical reactions they catalyze. The EC code consists of four numbers separated by periods. Those numbers represent a progressively finer classification of the enzyme, such that the fourth number generally represents the substrate

specificity. Strictly speaking, EC numbers do not specify enzymes, but enzyme-catalyzed reactions. If different enzymes catalyze the same reaction, then they receive the same EC number. The findings of Tian and Skolnick indicate that most (~90%) enzyme mutants will maintain enzyme function with sequence identities as low as 60% and in fact enzyme function does not generally *start* to diverge until the sequence identity is below 70% (See Tian and Skolnick, abstract, page 863). While these data relate to naturally occurring proteins, they are evidence of the amount of divergence that can occur within a protein sequence without having an effect on function. Thus, a skilled artisan would therefore expect be able to design a protein having at least 90% sequence identity to a disclosed reference sequence that would maintain function (e.g., capable of assembling into a transducing viral particle).

In response, the Examiner has pointed to evidence that "even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted." This is not disputed. However, at best this assertion is an indication that some variants will not be functional.

Notably, the Examiner cites a 1976 publication (Rudinger et al. 1976) to support the assertion that extensive trial and error experimentation would have been required to predict variant amino acid sequences for biologically active peptide hormones. However, even if this were a modern reference indicative of the current skill in the art, the painstaking experimental study described by the authors was not for predicting functional variants as posited by the Examiner. Rather, Rudinger et al. stated that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Thus, the painstaking study was not necessary to identify functional variants, but rather to predict the significance of particular amino acids to the biological activity of the peptide.

Likewise, the Examiner's assertion that "the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable" (citing Ngo et al., 1994) is misplaced. Ngo et al. were discussing the ability to computationally predict a tertiary structure of a protein based on its sequence, i.e., the ability to create an algorithm that could predict the structure of a protein based on its sequence, which is clearly not required to practice

the instant claims. Moreover, there is no evidence that modest changes in tertiary structure of a protein will necessarily alter the function of the protein. Again, at best, this is evidence that some variants will be non-functional due to the alterations of critical structural and/or catalytic domains.

Moreover, as argued in the prior response, many of these inactive variants will be predictable. For example, the skilled artisan is guided by the specification and knowledge in the art for AAV2 to make modifications by, for example, 1) conserving residues demonstrated to be important for AAV2 and 2) conserving residues that are variable between AAV2 and AAV4 and therefore likely to be important for unique tissue tropism.

Nevertheless, Applicants recognize that there is a line at which the predictability of obtaining a functional variant is so low that the skilled artisan would have to engage in undue experimentation to identify a variant within the genus. This would clearly be the case, for example, if the claim were to amino acids having 50% sequence identity to the reference sequence. However, the Examiner has taken the position that even 99% sequence identity is not enabled. Applicants therefore respectfully request that the Examiner identify the level of homology that would generally be enabled for an amino acid sequence. It stands to reason that some level of homology less than 100% would be enabled such that the predictability of identifying a functional variant is high enough that the experimentation required is not undue. Applicants respectfully assert that the skilled artisan can make and use the claimed vector systems without undue experimentation using amino acid sequences having at least 90% sequence identity to the reference sequences and therefore respectfully request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 3, 6-28, 38, 41 and 42 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Office Action notes that Claim 3 recites the limitation "the second vector" without antecedent basis for this limitation. Applicants have amended claim 2 to recite "a first and second vector," thus providing the necessary antecedent basis.

Conclusions

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

It is believed that no fee is due with this submission. However, the Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 14-0629.

Respectfully submitted,

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